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TOPIRAMATE EFFICACY IN TREATMENT OF CHILDREN WITH WEST SYNDROME

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The aim of our study was to assess prospectively the efficacy and tolerability of topiramate in treatment of children with West syndrome. Furthermore, we analyzed the effectiveness of topiramate in relation to etiology. Nineteen patients with West syndrome, aged 4 to 12 months, who were treated at the Pediatric Clinic, University Hospital of Split, Croatia between 2003-2005 were evaluated. The most common etiology was hypoxic-ischemic encepalopathy, which was the cause of seizures in 10 patients, followed by developmental cortical anomalies in 3 cases. Tuberous sclerosis was found in 2 patients and a porencephalic cyst was established in 1 patient. One patient was diagnosed with Down's syndrome and another with a metabolic disease. For 1 patient the etiology of West syndrome remained unknown. Ten patients out of 19 improved significantly with reduction of seizure frequency of 50-75%. In 5 patients the reduction of seizure frequency was over 75% and in 4 it was 25-50%. Topiramate is effective in the treatment of children younger than 12 months with West syndrome, especially in those with hypoxic-ischemic brain injury causing seizures.

Descriptors: TOPIRAMATE; SPASMS, INFANTILE; INFANT

INTRODUCTION

Topiramate is part of a group of so called "new antiepileptic drugs" with a wide spectrum of activity on seizures. It inhibits several anhydrase isosymes, modulates AMPA/kainite, $GABA_A$activated ion channels and voltage activated Na and Ca channels (1-3). Topiramate activates K conductance and inhibits depolarizing $GABA_A$ mediated responses (4). All these mechanisms contribute to the neuroprotective effect of topiramate by reducing excitatory amino acid release and ischemic depolarization (5). Moreover, it reduces calcium levels in the ischemic cells and increases GABAergic activity of the brain (6).

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Topiramate has demonstrated its effectiveness in both generalized and partial onset seizures (7-11). However, the object of these studies were older children and adults (12, 13), with the exception of infantile spasms (14, 15, 16). There are few reports regarding the treatment of children younger than 2 years with topiramate (17).

West syndrome is an age-related intractable epileptic syndrome, characterized by infantile spasms, developmental delay and hypsarrhythmia in EEG. It affects 1 out of 2000 to 4000 children. ACTH is the most effective therapy based on clinical experience (18). However, it is associated with a number of severe adverse effects (19, 20) and can be used only for short periods of time. Moreover, there is insufficient evidence regarding optimum dosage (21). Therefore, the need for new antiepileptic drugs that would be effective and safe in the treatment of children with West syndrome is of great importance.

We report our clinical experience in the treatment of 19 children with West syndrome, aged 4 to 12 months.

METHODS

We conducted this study to investigate the efficacy and tolerability of topiramate in 19 patients with West syndrome, aged 4 to 12 months, treated at the Paediatric Clinic, University Hospital of Split, Croatia, between 2003 and 2005. Gathered data included detailed personal and family medical histories, demographics, aetiology of seizures, psychomotor development and previous treatment with antiepileptic drugs. All patients underwent neuroimaging (CT and/or MRI) and EEG recordings. Complete blood count, biochemical analyses, acid-base status, screening for metabolic disorders, ultrasound of the urinary system and ophthalmologist exam were carried out. West syndrome was classified on the basis of clinical presentation and EEG results, in accordance with the International League Against Epilepsy (ILAE) classification of epileptic seizures and epileptic syndromes (22).

All patients were hospitalized and monitored continuously. After discharge they were controlled monthly for 6 mon-

Table 1. *Patient characteristics*
Tablica 1. *Osobine bolesnika*

Patient Bolesnik	Efficacy Učinkovitost	Spasm onset (months)	Etiology Etiologija	AEDs prior to topiramate
1.	75%	4	HIE	ACTH,VPA
2.	50-75%	5	HIE	ACTH
3.	25-50%	7	HIE	ACTH
4.	25-50%	6	Metabolic disease	ACTH,VPA
5.	50-75%	4,5	TS	ACTH,VGB
6.	75%	5	HIE	ACTH,VPA
7.	75%	5,7	Porencephalic cyst	ACTH,VPA
8.	50-75%	9	TS	ACTH,VGB
9.	75%	8	HIE	ACTH,VPA
10.	25-50%	9	Dev. cort anom.	ACTH,VPA
11.	50-75%	7	HIE	ACTH,VPA
12.	25-50%	12	Dev. cort anom.	ACTH,VPA
13.	50-75%	7	HIE	ACTH,VPA
14.	50-75%	8,5	Dev. cort anom.	ACTH,VPA
15.	50-75%	6	HIE	ACTH,VPA
16.	50-75%	3	Unknown	ACTH,VPA
17.	50-75%	5	HIE	ACTH,VPA
18.	75%	9	Down's syndrome	ACTH,VPA
19.	50-75%	5	HIE	ACTH,VPA

Legend
HIE = hypoxic-ischemic encephalopathy,
TS = tuberous sclerosis,
Dev. cort. anom = developmental cortical anomalies,
ACTH = adrenocorticotropic hormone,
VPA = valproat,
VGB = vigabatrin.

ths. The effectiveness of the treatment was assessed 6 months after its initiation.

Topiramate was started twice daily in a total daily dose 1 mg/kg, followed by weekly increments of 1 mg/kg until patient seizure free or the maximal tolerated dose or the maximal dose of 11 mg/kg/day was achieved. Parents and caregivers were trained to record seizure frequency and duration and adverse events. Response to topiramate therapy was assessed based on staff reports during hospitalisation and parents' diaries after discharge. The response to the therapy was classified in comparison with the baseline seizure frequency as follows: very efficacious (over 75% reduction of seizures), efficacious (50-75% reduction) and moderately efficacious (25-50% reduction).

RESULTS

Nineteen patients were included in the study, aged from 4 to 12 months, all diagnosed with West syndrome. The most common aetiology was hypoxic-ischemic encepalopathy, which was the cause of seizures in 10 patients, followed by developmental cortical anomalies in 3 cases. Tuberous sclerosis was present in 2 patients and a porencephalic cyst was established in 1 patient. One patient was diagnosed with Down's syndrome and another with metabolic disease. For one patient the aetiology of West syndrome remained unknown.

Before topiramate all patients were treated with ACTH (Synacten depo, 1 mg-100 IJ), which is the standard therapy in our country. In addition to this, 15 children were treated with valproat, while vigabatrin was used in 2 patients with tuberous sclerosis. Two patients with hypoxic-ischemic aetiology of seizures were treated with ACTH and topiramate from the beginning.

In 5 children the effect of the treatment was substantial since their condition improved by more than 75%. In 10 children we found a reduction of seizure frequency ranging 50-75% and in 4 patients reduction was 25-50%. We analyzed the effectiveness of the treatment according to aetiology. In children with hypoxic-ischemic aetiology of seizures, the effectiveness of topiramate was substantial, since in 3 children the reduction of seizures was more than 75% prior to treatment and in 6 children 50-75%. One patient's seizure frequency improved 25-50%. Children with Down's syndrome and porencephalic cyst improved more than 75%. The reduction of seizures in both patients with tuberous sclerosis was 50-75%. The effectiveness of topiramate in children with developmental cortical anomalies was not as satisfactory since the reduction of seizures was 25-50% in 2 children and 50-75% in one child. The child with metabolic disease improved 25-50% and one child with unknown aetiology improved 50-75%.

Topiramate was well tolerated and few adverse events were documented. Significant weight loss was registered in one patient and it was the cause of withdrawal of treatment. Hyperthermia due to secondary inhibition of enzyme carbon-anhydraze or dysfunction of sweat glands occurred in 1 patient. We documented loss of appetite in one child.

DISCUSSION

In this study we investigated the effectiveness of topiramate in children younger than 12 months with West syndrome. Several studies suggest that topiramate is an efficacious and safe option for treating a variety of seizure disorders in children younger than 2 years (14, 17, 23). About 50% to 60% of patients in this age group who had been treated with topiramate had seizure reduction of more than 50%. Patients diagnosed with West syndrome appear to be the best responders (23). Although topiramate demonstrated efficacy and tolerability in adults and older children (24, 25), there are not enough reports of the use of topiramate in infants and children younger than 2 years of age. In a study by Hosain et al, conducted on 15 children younger than 2 years of age and diagnosed with infantile spasms, three patients became spasm free (20%), five patients had a reduction in spasms greater than 50%, three patients had reduction in spasms of at least a 25%, and 4 patients did not respond (14). In an open-label, multicenter study by Watemberg et al. (17) conducted on 28 patients younger than 2 years of age topiramate was added as adjunctive therapy in 26 cases. The results showed that five of seven patients with mainly complex partial seizures improved, although only one had a reduction in seizure frequency of over

75%. Out of six children with simple partial seizures, one received topiramate up to 25 mg/kg/day for acute seizures due to meningitis and stroke and one child had a reduction in seizure frequency of over 50%. One patient with severe myoclonic epilepsy became seizure-free, one patient had a seizure frequency reduction of less than 50% and in four patients it had no effect. In seven of the children diagnosed with infantile spasms the improvement was over 50%. In our study, which was conducted on children with West syndrome, 10 patients out of 19 improved significantly, the reduction of seizure frequency was 50-75%. In 5 patients the reduction of seizure frequency was over 75% and in 4 it was 25-50%.

The initial dose was 1 mg/kg per day and was titrated gradually up to a mean dose of 7.9 mg/kg. The maximum dose was 11 mg/kg/TT per day. Most authors propose that the initial dose of topiramate should be 0.5 mg/kg-1 mg/kg per day and then progressively titrated 1mg/kg every week in order to improve tolerability (26). However, there is no consensus about the mean daily dose, 5-8 mg/kg per day are proposed, although some investigators used doses up to 29 mg/kg per day (16).

Antiepileptic drugs tend to have a higher clearance in young children. To achieve appropriate topiramate serum concentrations, younger children require higher dosages in comparison to those found in older children and adults (27). Due to this fact we administered higher doses, but we also adjusted topiramate dosage according to therapeutic response.

Topiramate is associated with a small number of adverse effects, which include hypohydrosis, somnolence, nervousness, weight loss, glaucoma, nephrolythiasis and metabolic acidosis (28-32). The results of our study are similar: one of our patients had acidosis, hyperamoniemia was found in one patient as well as a loss of appetite. One child was withdrawn from topiramate therapy due to significant weight loss.

Since some studies have reported that topiramate can affect language and cognition in adults (16), we assessed psychomotor development in all children. We could not register cognitive or language regression since most children had encephalopathy and cognitive impairment prior to topiramate treatment. This may be also due to the fact that this is the period of life when language is being developed, which makes it difficult to detect language regression. Valencia et al. suggest that the problem whether topiramate does induce this side effect or not could be clarified by using functional magnetic resonance imaging and positron emission tomography in the future while conducting studies with topiramate (23). This way we can assess the brain function of infants more directly.

There is a great need for further studies concerning the role of new antiepileptic drugs, topiramate being one of them, in treating West syndrome. Recent studies (33) suggest that topiramate can have anti-excitotoxic properties, because it protects against motor neuron degeneration. It enhances neuroprotection and reduces hemorrhagic incidence in focal cerebral ischemia (34). Experimental studies indicate that topiramate significantly reduces neuronal damage in animal models of global and focal ischemia and protects against cerebral ischemia (35-37). Moreover, when administered post-insult *in vivo* it is protective against selective hypoxic-ischemic white matter injury and decreases subsequent neuromotor deficits (38). To our knowledge, there are no reports of whether this can be applied in human models. In our study children with hypoxic-ischemic etiology of seizures showed better improvement than children with West syndrome induced by other etiology. However, we were limited by the small number of participants.

It remains unclear why topiramate is especially effective in this period of early childhood. It is well known that the immature brain has increased susceptibility to seizures and that seizures have different effects on the developing brain compared with the adult brain. It seems that the immature brain has a lower seizure threshold, and that can explain why idiopathic or cryptogenic seizures are relatively more common in the paediatric population. Some cellular and molecular mechanisms have an important role in epileptogenesis in the immature brain, including neurotransmitter receptors, transporters, and other molecules involved in neurotransmitter synthesis, degradation and signal transduction. Many of these factors can promote epileptogenesis by disturbing the excitatory/inhibitory balance during development. Molecules that have been the object of interest for scientists include glutamate receptors, $GABA_B$ receptors, glutamate and GABA transporters, neuropeptides and adenosine (39-43). It has been demonstrated that topiramate has an effect on some of these mechanisms (6, 7) in the immature brain, which could explain the effectiveness of topiramate in early childhood. Our study confirms that topiramate is effective in the treatment of children with West syndrome younger than 12 months, especially with hypoxic-ischemic induced seizures. However, further investigations are necessary to confirm our findings.

CONCLUSION

On the basis of our clinical experience, we conclude that topiramate should be taken into consideration when treating children with refractory epilepsy, who are younger than 12 months of age, because it suppresses the process of epileptogenesis. We were, however, limited by the relatively small number of patients. Large multicentric studies are needed to confirm this observation and prove the efficacy of topiramate and reveal its possible adverse effects.

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S a ž e t a k

UČINKOVITOST TOPIRAMATA U LIJEČENJU DJECE SA WESTOVIM SINDROMOM

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Cilj istraživanja bio je odrediti učinkovitost i podnošjivost topiramata u liječenju djece s Westovim sindromom te analizirati korelaciju učinkovitosti lijeka i etiologije bolesti. U istraživanje je bilo uključeno 19-ero djece s Westovim sindromom u dobi od 4 do 12 mjeseci života, koja su liječena u Klinici za pedijatriju KBC Split u razdoblju od 2003.-2005. godine. Najučestalija etiologija napadaja je bila hipoksično-ishemijska encefalopatija, koja je dijagnosticirana kod 10-ero djece. Kod 3-je djece riječ je bila o kortikalnoj anomaliji, dok je tuberozna skleroza bila uzrok napadaja u 2-je djece. Porencefalična cista je dijagnosticirana kod 1 djeteta, kao i Downov sindrom. Kod 1 djeteta uzrok napadaja je bila metabolička bolest, a kod 1 djeteta nije verificiran uzrok. Značajno poboljšanje je zabilježeno kod 10-ero od 19-ero djece, s redukcijom napadaja od 50-75%. Smanjenje učestalosti napadaja više od 75% zabilježeno je kod 5-ero djece, a u 4 slučaja 25-50%. Ovo istraživanje je pokazalo kako je topiramat učinkovit u liječenju djece s Westovim sindromom, mlađe od 12 mjeseci, osobito ako je riječ o hipoksično-ishemijskoj etiologiji bolesti.

Deskriptori: TOPIRAMAT; GRČEVI, DJECA

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